UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,892	01/03/2001	Leonid A. Yakubov	PANA-0002	1372

34132 7590 06/16/2005

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,892	YAKUBOV, LEONID A.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-20,22,31 and 43-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-20,22,31 and 43-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 48 is objected to because of the following informalities: claim 48 recites "does not cancer" in the third to last line of each claim. This phrase is grammatically incorrect; the phrase lacks a verb, e.g. -- have--.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 & 112

Claims 48-54 remain rejected and claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant asserts that the amendment overcomes the rejection. However, the new matter still appears in the claim (claim 48, at line 10).

Claims 1-8, 10-20, 22 and 31 remain rejected rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons of record set forth in the Office action of 9/28/04.

Claims 1-8, 10-20, 22 and 31 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments filed 3/28/05 have been fully considered but they are not persuasive. Referring to page 7 of the Office action of 9/28/04, Applicant asserts (page 11) that the grounds of rejection based upon the saturability of DNA binding to a cell is mistaken because binding is a continuing dynamic process, and that the calculation that a cell binds 3000 molecules is mistaken because lambda DNA (48,500 bp) was used. Applicant has presented no evidence or reasoning to support these assertions. It is unclear that saturation of cells *in vivo* would even occur, i.e. unclear that one could deliver sufficient DNA to cells *in vivo* to reach saturation. Bennett disclosed that DNA binding was saturable and that the cells bound about 3000 molecules. The Examiner did not calculate this. The calculations to which Applicant refers are directed first to the very low fraction of total genomic DNA fragments that can be expected to carry a desired allele to replace a given mutation and comparing that with the number of molecules of DNA one expects to be taken up by a cell, and the very low number of cells that undergo homologous recombination even when the DNA is non-limiting and all the donor DNA are fragments target the mutation, rather than being a very minor fraction of the donor DNA. The point of the calculation was only to show that one would expect the frequency of desired recombination events would be extremely low, and much lower than expected when the mutation is known and all donor DNA targets the known mutation. Applicant then asserts, again without

evidence or rationale, that one would accept from the teachings of Yanez, Porter and Riele that the invention was credible.

Applicant asserts (page 11) without explanation that nothing in Gilchrist would give reason to doubt the credibility of the claimed invention. However, the results of Gilchrist show that administration of DNA *in vivo* can have unforeseen effects that clearly do not involve homologous recombination. Consequently, one would have reason to doubt claims that the unexpected results described in the specification could be explained as necessarily involving homologous recombination.

Applicant argues that Ledoux (1965) does not describe the unsuccessful attempts (with one never-repeated exception) to transform animals in the prior art as delivering DNA according to the present invention. Other than the size of the DNA, which Ledoux (page 234) does not disclose, it is unclear what Applicant is referring to. The prior art and claimed methods both involve administering DNA extracted from others of the same species. Given that reducing the size of the DNA molecules to the size recited in the claims requires intentionally much harsher treatment than would be obtained by standard methods for isolating DNA, and given that the efficiency of homologous recombination between transforming donor DNA and cellular DNA was known to increase exponentially with increasing length of the donor DNA (see Yanez), one would not expect the claimed method to be more effective than that described in the prior art; quite the contrary, one would expect the claimed method to be less effective.

Applicant argues (page 12) that despite the all of the negative teachings in the prior art: Bearn reporting a failure to detect any transformation using DNA of a pigmented rat resulting in a phenotypic change in albino rats; Yoon reporting that uptake of homologous DNA by cells in

mice is so inefficient that if transformation were to occur, it would be at the level of spontaneous mutation; Karpfel reporting that *in vivo* administration of homologous DNA and even isogenic DNA is mutagenic, consistent with the known mutagenic effect of homologous DNA administered to cultured cells; and the results in Wilczok (1965) and Ledoux (1970) that the protective effect of DNA administered to lethally irradiated animals did not depend on homology between the donor DNA and the animal's genomic DNA, i.e. homologous recombination is not responsible for the effect; and the teachings of Pfeiffer that would suggest to one of skill in the art that non-homologous recombination is a more likely explanation for the protective effect (if recombination is involved at all); cited in the rejection, that this prior art did not teach that *in vivo* transformation cannot work or that one of skill in the art would find the claimed invention incredible.

However, the rejection is not based upon the conclusion from the prior art that *in vivo* transformation of animals using genomic DNA from another of the same species would not work at all, i.e. that homologous recombination between donor DNA and the cell genome in a few rare cells would not occur. Rather, the prior art suggests that if such homologous recombination occurs, the process is too inefficient to be useful for treating disease, and is more likely to be mutagenic itself.

Applicant argues (page 13) that using chimeraplasts to correct a undesired mutation at high frequency was at first believed credible, despite later experimental evidence showing that at best it was very inefficient if it worked at all, just like other gene correction methods based on homologous recombination (Taubes, 2000). However, Taubes disclosed that many in this art were skeptical from the beginning and that their skepticism was well founded. Also, Taubes

discloses one of skill in this art would require "iron clad" evidence before accepting claims of *in vivo* gene correction at useful levels. Direct tests of methods that were very similar, if not identical, to the claimed method had failed, as disclosed for example in Ledoux (1965) and Bearn. The instant specification does not provide the "iron clad" evidence that one of skill in this art would require.

With respect to ¶ 5 of the declaration filed 6/20/03, Applicant asserts without explanation that the Examiner's suggestion that illegitimate recombination was also a possible explanation of the results was pure speculation and without merit. No evidence is presented that homologous recombination was responsible for the effect seen. This is pure speculation on Applicant's part. Also, the prior art of record indicates that illegitimate recombination, i.e. mutagenesis, is far more common than homologous recombination in mammals.

With respect to ¶ 6 of the declaration, the Examiner had questioned whether the *in vitro* conditions employed with the cultured cells could be duplicated *in vivo*. Applicant points out that the specification teaches that continuous or multiple administration can be used to maintain DNA titers. However, the specification does not present evidence that the literal bathing of cultured cells in DNA could even be approached *in vivo* much less maintained. As disclosed in Kawabata et al., naked DNA administered to mice by intravenous injection is rapidly degraded not only in the blood (half-life of 10 min.), but rapidly cleared from the blood by non-parenchymal cells in the liver and further degraded by the liver. About 70% of input DNA was cleared from plasma within 5 min. According to Kawabata, the rapid clearance and degradation of DNA appears to be mediated by Kupffer and liver endothelial cells involving scavenger receptors on these cells.

With respect to the apparent magnitude of correction, the Examiner noted that the results in the declaration were "suspect" in view of the prior art, not similar in magnitude. Applicant asserts Yanez disclosed that small fragment homologous replacement had a much higher frequency, but does not indicate where in Yanez. If Applicant is referring to the last paragraph on page 153, col. 2, and page 154, col. 1, Yanez indicates that the use of simple nucleic acids with small regions of homology are unlikely to be efficient (page 153), and the one report of higher efficiency (1 in 100 cells) was at odds with earlier prior art reports and that explanations of the higher reported efficiency remained unclear (page 154, col. 1, ¶ 2). With respect to the PCR assay, the size of the amplified fragment is as short or shorter than the minimum sized fragment of donor DNA, not a "relatively long DNA therapeutic fragment" as indicated by Applicant. As a result, one cannot conclude that the apparently high frequency of correction was due to recombination in many cells, or some other reason. This result is similar to that reported in Yanez on page 153 that was at odds with other prior art.

Applicant argues that the inefficiency observed by Szybalski may have been due to the short time of exposure or the molecular weight of the DNA. However, there is no evidence of record to suggest that the time of exposure was short relative to the time it would have taken the cells to take up the donor DNA. As to the size, one may conclude that the size of the fragments were larger than that used in the claimed invention. Szybalski discloses that gentle conditions were used to prepare the DNA with high specific transforming activity, i.e. to preserve larger size; unlike the claimed method where DNA is prepared by standard techniques with no effort to decrease breakage and then treated with harsh conditions in order to reduce the size. The prior art had taught that increasing size of donor DNA increased homologous recombination

exponentially with the maximum seen at 14,000 bp (Yanez), and Szbalski teaches that high transforming activity correlated with gentle isolation techniques, i.e. longer donor DNA. One would expect the harsh treatment of donor DNA to reduce homologous recombination efficiency, not increase it.

Applicant merely indicates that ¶s 7-11 of the declaration were improperly dismissed in the previous Office action, rather than rebutting the statements made in the Office action. Whether a therapeutic result was seen in these experiments is not the issue. The claimed invention requires that any therapeutic effect be the result of homologous recombination between donor DNA and the genome of recipient cells. No evidence is presented in ¶s 7-11 that homologous recombination was involved. As pointed out, the results in ¶ 7 were similar to those in the prior art (Wilczok and Ledoux (1970)), where donor DNA provided a protective effect from lethal irradiation independent of whether the donor DNA was homologous, i.e. homologous recombination is unlikely to be the explanation.

Claim 48-52 and 54 remain rejected and claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 9/28/04, because the specification, while being enabling for treating an individual exposed to ionizing radiation, does not reasonably provide enablement for treating individuals exposed to other mutagenic stimuli. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant's arguments filed 3/28/05 have been fully considered but they are not persuasive. Applicant argues that the claims are not limited to any particular mechanism of action, and that

assertions made in the specification must be accepted as true unless evidence and reasoning is presented that would cast doubt on the truth of the assertion. Applicant argues that since the evidence presented in the rejection is based upon an unclaimed proposed mechanism that it does not apply to the claimed invention. Applicant concludes by asserting, without explanation or support, that the "evidence of record overwhelming supports the conclusion that the invention ... is enabled."

In response, the rejection set forth evidence that the premise behind the claimed invention was that the method would correct or prevent mutations made by mutagenic stimuli by homologous recombination was doubtful. Since no other plausible basis for the mechanism of action of the treatment other than correction of mutations is disclosed and the specification does not provide working examples that the method would have any beneficial effect, the objective truth of the assertions made in the specification are in doubt. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them - *Ex parte Sudilovsky*, 21 USPQ2d 1702, 1705 (BPAI 1991); *In re Novak*, 134 USPA 335 (CCPA 1962); *In re Fouche*, 169 USPQ 429 (CCPA 1971).

Claim Rejections - 35 USC § 102

Claims 43-53 remain rejected and claims 58-60 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sekiguchi et al., US 3,803,116 for the reasons of record set forth in the Office action of 9/28/04, and the

additional reasons set forth below. The 2000/2001 Sigma Catalog (page 319) is provided as evidence that at the time the invention human placental DNA was commercially available.

Sekiguchi et al. teaches a method for treating cancer patients, e.g. humans, being treated with ionizing radiation that involves administration of genomic DNA isolated from individuals, e.g. from fish sperm or mammalian organs, alone or complexed with polyamines or polyamino acids. The DNA is reduced in size to the range of 200,000 to 500,000 MW, which is approximately 300-800 base pairs in length. The goal of the treatment is to reduce the deleterious side effects of the radiation treatment, e.g. leucopoenia. In a working example (col. 3-4), lethally-irradiated mice were treated with free herring sperm DNA or herring sperm DNA complexed with spermidine. The treatment was effective to extend the average lifespan of the irradiated mice, and the fraction surviving past 30 days. In this case, lethality is a condition associated with the mutagenic stimuli.

The claims have been amended to limit the method to treatment of humans with human DNA. New claims 58-60 are directed to limitations on dosage and dose schedule.

With respect to dosage, Sekiguchi (col. 3) teaches using a dose of 25 μg/g body weight, which for a 50-100 kg human would be a dose of 1.25 –2.5 g of DNA per dose, administered several times a week. Sekiguchi teaches that using human DNA to treat humans would be difficult due to obtaining human tissue from which the DNA could be made (in 1974). Non-human DNA is preferred by Sekiguchi based purely on practical considerations in obtaining sufficient quantitites. Sekiguchi notes that using non-human DNA carries the risk of hereditary damage, which is a reason to use human DNA if it can be obtained. See col. 1, line 63, to col. 2, line 11). The 1993 Sigma Molecular Biology Catalog and 2000/2001 Sigma Catalog show that at

the time the instant invention was made, that ultra-pure human placental DNA was commercially available, and could therefore be used in the method of Sekiguchi to avoid the risk of hereditary damage from using non-human DNA. The 2000/2001 Sigma Catalog is provided to show the price at about the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1632